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National Toxicology Program; Chemicals (20) Nominated for Toxicological Testing; Request for Comments

SUMMARY: On January 21, 1981, the Chemical Evaluation Committee of the **National Toxicology Program** (NTP) reviewed 20 chemicals nominated for toxicological testing and made recommendations as to types of testing to be performed. The evaluation of nominated chemicals by the Committee constitutes an integral part of the NTP chemical nomination and selection process. This notice lists the 20 chemicals evaluated by the Committee, requests public comment on these chemicals, and summarizes the present NTP chemical nomination and selection process.

FOR FURTHER INFORMATION AND SUBMISSION OF COMMENTS, CONTACT:

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TEXT: SUPPLEMENTARY INFORMATION:

I. Background

The chemical nomination and selection process is critical to the effective long-term operation of the NTP with respect to both the testing of chemicals using current methodologies and the validation of new methodologies.

The selection process has evolved significantly since the inception of the NTP in November, 1978. The NTP Board of Scientific Counselors, as one of its first actions in January, 1980, formed a subcommittee on chemical nomination and selection to evaluate the process and make recommendations for its improvement. Following a subcommittee meeting at which representatives from member agencies of the NTP, industry, labor, and a public interest group discussed various schemes for setting priorities for selecting chemicals to test, the Board examined the NTP chemical selection process and and held extensive discussions with NTP staff. At its October, 1980 meeting, the Board of Scientific Counselors adopted recommendations modifying the process, which included provisions for public review of the nominated chemicals. The recommendations of the Board were accepted and are being implemented.

The following discussion briefly summarizes the current NTP chemical nomination and selection process.

II. NTP Chemical Nomination and Selection Process

Member agencies of the National Toxicology Program and other sources (e.g., other federal agencies, public, labor, industry) submit to the NTP nominations of chemicals for various types of toxicological testing. The nominating agency or source is asked to submit the name of the chemical and the particular toxicological tests desired, and to provide the rationale for testing, and available background data on production, use, exposure, environmental occurrence, and extent of toxicological characterization in a supporting summary document.

All nominated chemicals are first referred to the NTP Technical Information Section to determine which chemicals have already been tested, are on test or scheduled for test, or have been previously considered and rejected for testing by the NTP or its predecessors. This involves preliminary examination of the nominations with minimal searches of exist-

ing on-line data bases and reference books. The nominations and background information are then forwarded to the Chemical Review staff at the National Center for Toxicological Research (NCTR) who assess the relevant data and prepare Executive Summaries of this information on chemicals nominated for testing. (Executive Summaries are not prepared for chemicals nominated only for mutagenicity testing.) Included in each Executive Summary are sections with the following titles: Chemical Agent, Surveillance Index, Human Exposure and Health Effects, Research Hypothesis to be Tested, Categories of Study, and Source of and Reason for Nomination.

The Chemical Review staff then send the draft Executive Summaries to the Chemical Evaluation Committee (CEC), which is composed of representatives from the Consumer Product Safety Commission (CPSC), Environmental Protection Agency (EPA), Food and Drug Administration (FDA), Occupational Safety and Health Administration (OSHA), National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), National Institute for Occupational Safety and Health (NIOSH), National Center for Toxicological Research (NCTR), and National Toxicology Program (NTP). The CEC evaluates the draft Executive Summaries and recommends the types of testing to be performed. Primary and secondary reviewers are assigned to each chemical after consideration of the nature of exposure so that, to the extent possible, appropriate regulatory concerns will be addressed. Each member is requested to search data bases unique to his or her agency for further information on the nominated chemicals (and structurally related compounds) in order to improve the evaluation process.

At the CEC meeting the primary reviewer for each chemical summarizes the data on that chemical and makes recommendations as to testing. The secondary reviewer presents additional information, where available, and also discusses the merits of testing the compound. Following a general discussion, the Committee votes on the recommended types of testing and assigns priorities for types of testing. The recommendations are based upon whether the chemical satisfies one or more of the eight NTP chemical selection principles. The Chemical Review Staff revises the Executive Summaries accordingly.

The list of chemicals recommended for mutagenicity testing is entered into the NTP Environmental Mutagenesis Test Development Program. CEC recommendations for mutagencicity testing are not subject to the further review phases which chemicals recommended for other types of testing must undergo.

A Federal Register Notice is published which lists the chemicals reviewed by the CEC and the recommended types of testing. The notice also solicits comments from interested parties as well as information on completed, ongoing and planned testing in the private sector. Responses are requested within 30 days of the date of publication. The list of chemicals is also published in the NTP Technical Bulletin along with a request for comments. These steps are taken to enable outside individuals and groups to participate in the NTP evaluation process.

The revised Executive Summaries and public comment on the nominated chemicals are then forwarded to the Board of Scientific Counselors for review. The Board subsequently meets to evaluate the submitted data and ranks the chemicals for testing.

The Chemical Review Staff then incorporates both the Board's ratings and comments and pertinent public input into final Executive Summaries which are submitted to the Executive Committee. The Executive Committee decides whether to test, defer or delete each of the nominated chemicals for the various types of testing.

Following Executive Committee selection, the NTP Steering Committee meets to refer the chemicals to one or more of the three organizational units participating in the NTP, namely the National Institutes of Health (NIH), NIOSH, and NCTR. At this point certain approved chemicals may be identified as not being appropriate candidates for testing as a result of technical or budgetary reasons. Also in some cases, public input describing adequate outside testing may only have been submitted following Executive Committee decision. Such chemicals are then returned to the Executive Committee with the rationale for reconsideration.

All chemicals selected in this process are then tested as time and resources permit.

III. Twenty Chemicals Nominated for NTP Testing

On January 21, 1981, the CEC held its first meeting utilizing the format recommended by the NTP Board of Scientific Counselors for evaluation of nominated chemicals. Twenty chemicals nominated for NTP testing during 1980 were reviewed and recommendations for testing were developed. The following table lists the chemicals, the Chemical Abstracts Service (CAS) registry numbers, and the types of testing recommended by the CEC:

Chemical	CAS No.	Committee recommendation
1. Acetic anhydride	108-24-7	Mouse Strain A lung adenoma assay, Pharmacokinetics, Acylating ability.
2. Brucine	357-57-3	Mutagenicity, Dermal absorption study.
3. C.I. Direct Black 19	6428-31-5	Deferred until completion of Dye, Class Study by Chemical Selection, Working Group of National Cancer Institute.
4. C.I. Direct Blue 15	2429-74-5	Part of NTP benzidine dye testing initiative;* No additional testing recommended.
5. C.I. Direct Red 2	992-59-6	Part of NTP benzidine dye testing initiative;* No additional testing recommended.
6. C.I. Direct Red 39	6358-29-8	Part of NTP benzidine dye testing initiative;* No additional testing recommended.
7. C.I. Vat Blue 1	482-89-3	Mutagenicity, Skin absorption and distribution, Carcinogenicity, Reproductive Effects.
8. Cyclohexane	110-82-7	Mutagenicity, Neurotoxicity, Reproductive effects.
9. 1,3-Dichloro-5, 5-dimethylhydantoin	118-52-5	Skin absorption and distribution, Carcinogenicity, Reproductive effects.
10. Dodecenyl-succinic Anhydride	25377-73-5	Mutagenicity, Pharmacokinetics.
11. Ergonovine	60-79-7	Mutagenicity *(Salmonella* assay only).
12. Ergotamine	113-15-5	Battery of short term tests including *Salmonella* assay.
13. Methyl bromide	74-83-9	Carcinogenicity (inhalation).
14. Methyl fluoro-sulfonate	421-20-5	Mouse Strain A lung adenoma assay.
15. Methyl isocyanate	624-83-9	Mutagenicity.
16. Noscapine	128-62-1	Mutagenicity.
17. Piperidine	110-89-4	No testing recommended.
18. Tetrafluoroethyl ene	116-14-3	Mutagenicity, Carcinogenicity.
19. 4,4-Thio-bis (6-tert-butyl-m-cresol)	96-69-5	Mutagenicity, Uptake and distribution, Carcinogenicity, Reproductive effects.
20. Trimethyloxonium hexachloroantimonate	54075-76-2	Mutagenicity, mouse Strain A lung adenoma assay.

*In collaboration with EPA, CPSC, and OSHA, the NTP developed a toxicological testing initiative on a group of dyes based on benzidine and the benzidine congeners o-tolidine and o-dianisidine. Tests to be performed on representative dyes include genotoxicity studies, pharmacokinetic and metabolism studies, and carcinogenicity bioassays. C.I. Direct Red 2, C.I. Direct Red 39 and C.I. Direct Blue 15 are all a part of the testing initiative.

IV. Request for Public Comment

Interested parties are requested to submit pertinent information which will aid the NTP Executive Committee in deciding whether to select, defer, or reject these chemicals for testing. Of particular relevance are the following types of data:

(1) Completed, ongoing and/or planned toxicological testing in the private sector including detailed protocols and, in the case of completed studies, resultant data.

(2) Modes of production, present production levels and potential for occupational exposure.

(3) Uses and resulting exposure levels, where known.

(4) Results from toxicological studies of structurally related compounds.

Kindly submit such information in writing by (thirty days after date of publication). Submissions received after this date, however, will be accepted and utilized where possible.

Dated: April 7, 1981.

David P. Rall,

Director, National Toxicology Program.
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